



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/733,212

12/11/2003

Donald W. Kufe

GENU:009USD1/10717456

7998

32425 7590 05/28/2009  
FULBRIGHT & JAWORSKI L.L.P.  
600 CONGRESS AVE.  
SUITE 2400  
AUSTIN, TX 78701

EXAMINER

HILL, KEVIN KAI

ART UNIT

PAPER NUMBER

1633

MAIL DATE

DELIVERY MODE

05/28/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b>	<b>Application No.</b> 10/733,212	<b>Applicant(s)</b> KUFE, DONALD W.	
	<b>Examiner</b> KEVIN K. HILL	<b>Art Unit</b> 1633	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 11 May 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 1 months from the mailing date of the final rejection.  
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b) ☐ They raise the issue of new matter (see NOTE below);  
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
 5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.  
 6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
 7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
 The status of the claim(s) is (or will be) as follows:  
 Claim(s) allowed: \_\_\_\_\_.  
 Claim(s) objected to: \_\_\_\_\_.  
 Claim(s) rejected: 1,5,7-9,13,15-17 and 22-26.  
 Claim(s) withdrawn from consideration: 2-4,6,10-12 and 14.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.  
 12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_  
 13. ☒ Other: See Continuation Sheet.

/Anne Marie S. Wehbe/  
 Primary Examiner, Art Unit 1633

Continuation of 5. Applicant's reply has overcome the following rejection(s):  
The prior rejection of Claim 13 under 35 U.S.C. 112, second paragraph, is withdrawn in light of Applicant's amendments to the claims.

The prior rejection of Claims 25-26 under 35 U.S.C. 112, first paragraph, is withdrawn in light of Applicant's amendments to the claims to limit the scope of the source of phosphate ions to ATP.

Continuation of 11. does NOT place the application in condition for allowance because: Claims 1, 5, 7-9, 13, 15-17 and 22-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Mol. Cell Biol. 18(12): 7216-7224, 1998, \*of record in IDS) in view of Yamamoto et al (J. Biol. Chem. 272(19): 12492-12494, 1997; \*of record) and Barker et al (U.S. Patent 5,851,775), as evidenced by Zrihan-Licht et al (FEBS Letters 356(1):130-136, 1994; \*of record).

#### Response to Amendment

The Kufe Declaration filed on May 11, 2009 under 37 CFR 1.131 is sufficient to overcome the evidentiary reference Li et al (J. Biol. Chem. 276(38):35239-35242, 2001; \*of record in IDS). However, the fact remains that in human cancers (Li, 1998; Yamamoto, Barker) which express MUC1, MUC1 associates constitutively with the epidermal growth factor receptor (EGF-R) which phosphorylates MUC1 at the YEKV site. Thus, the endogenous MUC1 test agent will necessarily be phosphorylated at the YEKV site as part of the natural cell biology and metabolism of the cancer cells.

#### Response to Arguments

Applicant argues that:

- a) Neither Li (1998), Yamamoto or Barker teach or suggest that phosphorylation of a YEKV site increases binding of MUC1 to  $\beta$ -catenin;
- b) there is no information in Li (1998) to teach or suggest that the MUC1 test agent equivalent in Li (1998) was phosphorylated at a YEKV site. Nor would this be inherent, as it is possible for a YEKV site to not be phosphorylated;
- c) Li (1998) teaches that it is phosphorylation of a serine residue that affects interaction of MUC1 with  $\beta$ -catenin;
- d) Li (1998) teaches that it is phosphorylation of a serine residue that affects interaction of MUC-1 with  $\beta$ -catenin, and thus teach away from the invention.
- e) Yamamoto does not provide any teaching or suggestion concerning a MUC1 test agent phosphorylated at a YEKV site;
- f) Yamamoto concerns certain studies demonstrating that DF3 (MUC1) binds directly to  $\beta$ -catenin and that the SXXXXXSSL motif in DF3 is responsible for this interaction;
- g) Neither Li (1998) nor Yamamoto teach that the  $\beta$ -catenin test agent is a peptide fragment.
- h) while Zrihan-Licht discloses that MUC1 proteins are "extensively phosphorylated" and that phosphorylation occurs "primarily on tyrosine residues" it does not specifically teach phosphorylation of the YEKV site of MUC1. MUC1 protein includes 13 tyrosine residues, and there is no information in this reference or in any of the other references to suggest that this particular tyrosine residue, out of all of the amino acids of MUC1, is critical for binding to  $\beta$ -catenin; and
- i) Zrihan-Licht teaches that other residues may undergo phosphorylation, including serine residues. Zrihan-Licht teaches that the sequence YEEV is important for interaction with SH2 domain-containing tyrosine kinases, thus teaching away from the importance of a YEKV site.

Applicants arguments have been fully considered, but are unpersuasive.

With respect to d), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Li (1998) teach that there are two tyrosine residues that immediately flank the MUC1 SXXXXXSSL motif to which  $\beta$ -catenin binds (pg 7218, Figure 2), and teach that modification of the serine in the test peptide TDRSPYE, wherein the tyrosine residue of the test peptide is the tyrosine of the YEKV motif, reduced, but did not eliminate the interaction between MUC1 and  $\beta$ -catenin (pg 7221, col. 2), and thus, signals other than GSK-3 $\beta$ -mediated phosphorylation may contribute to regulation of the MUC1- $\beta$ -catenin complex. Therefore, when Li (1998) is considered in its entirety, Li neither teaches away, discredits or otherwise discourage the ordinary artisan from determining the role tyrosine phosphorylation may play in the interaction between MUC1 and  $\beta$ -catenin. Furthermore, Yamamoto et al teach that "Whereas the cytoplasmic domain of MUC1 is phosphorylated on tyrosine, it is not known if tyrosine sites influence binding of catenins to the serine-rich motif." (pg 12494, col. 1). Thus, Yamamoto et al suggest the phosphorylation of one or more of the seven tyrosine residues in the MUC1 cytoplasmic domain to pursue this possible regulatory feature, wherein the YEKV site is immediately adjacent to the serine-rich motif. Thus, at the time of the invention, those of ordinary skill in the art were motivated to determine if other phosphorylated residues in the MUC1 cytoplasmic domain were responsible for the interaction between MUC1 and  $\beta$ -catenin.

With respect to g), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Applicant appears to have overlooked that Barker teaches the use of  $\beta$ -catenin peptide fragments.

With respect to i), Applicant appears to have overlooked that Zrihan et al "emphasized" that the tyrosine residues of the MUC1 cytoplasmic domain are "postulated" to interact with SH2 domain containing proteins and "represent only presumptive docking sites for SH2 domain containing proteins" (pg 133, col. 2). While the pYEEV motif has been shown to be one of the most preferred sequences for interaction with a number of SH2 domain containing cytoplasmic tyrosine kinases, it does not teach away from all other tyrosines.

With respect to a-c, e, f, h), Applicant is respectively reminded that the MUC1 cytoplasmic domain contains only 7 tyrosine residues, not 13. The tyrosine phosphorylation of MUC1, and the YEKV site in particular, necessarily flows from the signal transduction pathways activated in the cancer cells of Li et al (1998), Yamamoto et al and Barker. Yamamoto et al teach that "Whereas the cytoplasmic domain of

MUC1 is phosphorylated on tyrosine, it is not known if tyrosine sites influence binding of catenins to the serine-rich motif.” (pg 12494, col. 1). Thus, Yamamoto et al suggest the phosphorylation of one or more of the seven tyrosine residues in the MUC1 cytoplasmic domain to pursue this possible regulatory feature, wherein the YEKV site is immediately adjacent to the serine-rich motif. Li (1998) teach that there are two tyrosine residues that immediately flank the MUC1 SXXXXXSSL motif to which  $\beta$ -catenin binds (pg 7218, Figure 2), and teach that modification of the serine in the test peptide TDRSPYE, wherein the tyrosine residue of the test peptide is the tyrosine of the YEKV motif, reduced, but did not eliminate the interaction between MUC1 and  $\beta$ -catenin (pg 7221, col. 2), and thus, signals other than GSK-3 $\beta$ -mediated phosphorylation may contribute to regulation of the MUC1- $\beta$ -catenin complex. Thus, the knowledge generally available to the ordinary artisan at the time of the invention provided the understanding that phosphorylation on tyrosine residues is a key step in intracellular signal transduction pathways mediated by membrane proteins, that the instantly recited YEKV site is one of two possible tyrosine residues that flank the MUC1 motif to which  $\beta$ -catenin binds, that the instantly recited YEKV site exists between the GSK3 $\beta$  binding motif and the  $\beta$ -catenin binding motif, and that serine phosphorylation of the GSK3 $\beta$  binding motif was insufficient to completely eliminate  $\beta$ -catenin binding. Thus, the data in the art strongly suggests, and it would be common sense for the ordinary artisan, to determine whether or not the phosphorylation of the YEKV site was a determining factor for the ability of  $\beta$ -catenin to bind MUC1.

Thus, absent evidence to the contrary, the Examiner maintains the position that invention as a whole is prima facie obvious because it would have been obvious to one of ordinary skill in the art to try a MUC1 test agent comprising a phosphorylated YEKV site in a method to identify a compound that inhibits the binding between a tumor progressor test agent such as  $\beta$ -catenin and a MUC1 test agent because “a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product not of innovation but of ordinary skill and common sense.” An artisan would be motivated to try a MUC1 test agent comprising a phosphorylated YEKV site in a method to identify a compound that inhibits the binding between a tumor progressor test agent such as  $\beta$ -catenin and a MUC1 test agent because, at the time of the invention, those of ordinary skill in the art were already aware that:

- i) the cytoplasmic domain of MUC1 comprising SEQ ID NO:1 is extensively phosphorylated on tyrosine residues,
- ii) there are but seven, immediately envisioned, tyrosines in the MUC1 cytoplasmic domain capable of being phosphorylated,
- iii) phosphorylation on tyrosine residues is a key step in signal transduction pathways mediated by membrane proteins, e.g. MUC1,
- iii) the MUC1 cytoplasmic domain possesses a peptide motif that mediates binding to  $\beta$ -catenin,
- iv) the YEKV (SEQ ID NO:11 within SEQ ID NO:1) peptide motif is immediately adjacent to the MUC1 peptide motif to which  $\beta$ -catenin binds, and
- v) Yamamoto et al teach that “Whereas the cytoplasmic domain of MUC1 is phosphorylated on tyrosine, it is not known if tyrosine sites influence binding of catenins to the serine-rich motif.” (pg 12494, col. 1). Thus, Yamamoto et al suggest the phosphorylation of one or more of the seven tyrosine residues in the MUC1 cytoplasmic domain to pursue this possible regulatory feature.

Continuation of 13. Other:

Applicant's response and amendments, filed May 11, 2009, to the prior Office Action is acknowledged.

Applicant has cancelled Claims 18, 20-21 and 27, withdrawn Claims 2-4, 10-12 and 14, and amended Claims 9, 13, 25 and 26.

The reply filed on May 11, 2009 is not fully responsive to the prior Office Action because of the following omission(s) or matter(s):

A. The amendments to the claims do not comply with the Revised Amendment Practice of 37 CFR 1.121 (See OG Notice 23 September 2003). Specifically, a list of all claims should be submitted, the text of withdrawn claims must be included in the listing of the claims and the text of canceled claims must be omitted.

§1.121 Manner of making amendments in applications.

(c) Claims. Amendments to a claim must be made by rewriting the entire claim with all changes (e.g., additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

(2) When claim text with markings is required. All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended," and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended," or "withdrawn" if also being amended, shall include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn- currently amended."

In the instant case, the correct status of Claim 25 is (Currently Amended).

Claims 2-4, 6, 10-12 and 14 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1, 5, 7-9, 13, 15-17, 19 and 22-26 are under consideration.

The prior objections to Claims 13 and 26 are withdrawn in light of Applicant's amendments to the claims.